

“Looks familiar, but I do not know who she is”

Borghesani, Valentina; Narvid, Jared; Battistella, Giovanni; Shwe, Wendy; Watson, C.; Binney, Richard; Sturm, V.; Miller, Zachary A; Mandelli, Maria Luisa; Miller, Bruce L; Gorno-Tempini, Maria Luisa

Cortex

DOI:

[10.1016/j.cortex.2019.01.006](https://doi.org/10.1016/j.cortex.2019.01.006)

Published: 01/06/2019

Peer reviewed version

[Cyswllt i'r cyhoeddiad / Link to publication](#)

Dyfyniad o'r fersiwn a gyhoeddwyd / Citation for published version (APA):

Borghesani, V., Narvid, J., Battistella, G., Shwe, W., Watson, C., Binney, R., Sturm, V., Miller, Z. A., Mandelli, M. L., Miller, B. L., & Gorno-Tempini, M. L. (2019). “Looks familiar, but I do not know who she is”: The role of the anterior right temporal lobe in famous face recognition. *Cortex*, 115, 72-85. <https://doi.org/10.1016/j.cortex.2019.01.006>

Hawliau Cyffredinol / General rights

Copyright and moral rights for the publications made accessible in the public portal are retained by the authors and/or other copyright owners and it is a condition of accessing publications that users recognise and abide by the legal requirements associated with these rights.

- Users may download and print one copy of any publication from the public portal for the purpose of private study or research.
- You may not further distribute the material or use it for any profit-making activity or commercial gain
- You may freely distribute the URL identifying the publication in the public portal ?

Take down policy

If you believe that this document breaches copyright please contact us providing details, and we will remove access to the work immediately and investigate your claim.

“Looks familiar, but I do not know who she is”:

The role of the anterior right temporal lobe in famous face recognition

Running title: **Famous faces processing in neurodegenerative syndromes.**

Valentina Borghesani, PhD¹, Jared Narvid, MD², Giovanni Battistella, PhD¹,
Wendy Shwe BA¹, Christa Watson, Psy.D^{1,3}, Richard J. Binney, PhD⁴, Virginia Sturm, PhD¹,
Zachary Miller, MD^{1,3}, Maria Luisa Mandelli, PhD^{1,3}, Bruce Miller, MD¹,
and Maria Luisa Gorno-Tempini, MD, PhD^{1,3}

¹ Department of Neurology, Memory and Aging Center, University of California, San Francisco, CA

² Department of Radiology and Biomedical Imaging, University of California, San Francisco, CA

³ Department of Neurology, Dyslexia Center, University of California, San Francisco, CA

⁴ School of Psychology, Bangor University, Gwynedd, Wales, UK

Correspondence to:

Valentina Borghesani, PhD
valentina.borghesani@ucsf.edu
Department of Neurology,
Memory and Aging Center,
University of California San Francisco
675 Nelson Rising Lane, Mission Bay Campus,
San Francisco, CA 94158, USA

Abstract

Processing a famous face involves a cascade of steps including detecting the presence of a face, recognizing it as familiar, accessing semantic/biographical information about the person, and finally, if required, production of the proper name. Decades of neuropsychological and neuroimaging studies have identified a network of occipital and temporal brain regions ostensibly comprising the ‘core’ system for face processing. Recent research has also begun to elucidate upon an ‘extended’ network, including anterior temporal and frontal cortex. However, there is disagreement about which brain areas are involved in each step, as many aspects of face processing occur automatically in healthy individuals and rarely dissociate in patients. Moreover, some common phenomena are not easily induced in an experimental setting, such as having a sense of familiarity without being able to recall who the person is. Patients with the semantic variant of Primary Progressive Aphasia (svPPA) often recognize a famous face as familiar, even when they cannot specifically recall the proper name or biographical details. In this study, we analyzed data from a large sample of 105 patients with neurodegenerative disorders, including 43 svPPA, to identify the neuroanatomical substrate of three different steps of famous face processing. Using voxel-based morphometry, we correlated whole-brain grey matter volumes with scores on three experimental tasks that targeted familiarity judgment, semantic/biographical information retrieval, and naming. Performance in naming and semantic association significantly correlate with grey matter volume in the left anterior temporal lobe, whereas familiarity judgment with integrity of the right anterior middle temporal gyrus. These findings shed light on the neuroanatomical substrates of key components of overt face processing, addressing issues of functional lateralization, and deepening our understanding of neural substrates of semantic knowledge.

Keywords: face processing, semantic knowledge, neurodegenerative disorders, primary progressive aphasia, voxel-based morphometry

Introduction

While usually occurring automatically and effortlessly, face processing is critical in many aspects of our daily life, and its breakdown is highly debilitating. When encountering someone we know, it is not uncommon to experience a sense of familiarity but fail to immediately recall relevant semantic attributes, or their name. Successful face recognition relies on a cascade of processes that are at least partially dissociable: from analyzing the apparently simple visual stimulus, to accessing rich semantic and biographical information. The early framework for person identification processing was significantly influenced by the cognitive model of Bruce and Young (Bruce and Young, 1986), which included two crucial steps. First, voice, face, and name information, processed in modality-specific units, lead to feelings of familiarity (e.g., *I know I have seen her before*). Second, the activation of so-called person identity node (PIN) enables identification and grants retrieval of person-specific semantic information (e.g., *she is the 1911 chemistry Nobel Prize winner*) (Ellis *et al.*, 1997; Gainotti, *et al.*, 2015). Functional neuroimaging evidence and lesion studies have enabled increasingly refined adaptations of the original cognitive model: several cortical areas, mostly in the temporal and occipital lobes, appear to play a key role in humans' unique face processing abilities (Gobbini and Haxby, 2007; Blank *et al.*, 2014). However, the precise anatomical localization of the different cognitive steps involved in face processing has yet to be fully determined.

Functional neuroimaging findings suggest a subdivision of this distributed network into a 'core' system responsible for primarily perceptual processing and an 'extended' network that underpins cognitive aspects of processing including accessing to person knowledge and making inferences about their state and intentions (Haxby *et al.*, 2000). Posterior occipital and temporal

regions, such as the fusiform face area (FFA), the occipital face area (OFA), and the posterior superior temporal sulcus (pSTS), appear to comprise core face processing system (Gobbini *and* Haxby, 2007; Natu *and* O'Toole, 2011). Proceeding along a posterior-to-anterior axis, responses become increasingly tuned to more complex feature combinations and abstracted from low-level perceptual features, ultimately ending with higher-order semantic processing within the anterior temporal lobe (ATL) (Rajimehr *et al.*, 2009; Brambati *et al.*, 2010; Binney, Parker & Lambon Ralph, 2012; Collins *and* Olson, 2015). Recently, the adoption of information-based pattern analyses has led to the observation that face identity information can be read out from (right anterior) temporal and occipital cortex (Kriegeskorte *et al.* 2007, Nestor *et al.*, 2011, Verosky *et al.* 2013). However, functional neuroimaging studies suffer from three key limitations. First, disentangling the neural substrates of lexical, semantic and familiarity-related processes is nontrivial given that the presentation of a known face presumably triggers all three automatically. Second, they offer correlational evidence at best: they do not allow assessment of whether a given region activation is necessary for a given process or plays only an ancillary role. Third, conventional EPI techniques used for fMRI are vulnerable to artefacts that greatly impact sensitivity to signal in the ATL, hindering investigation of this area (Devlin *et al.*, 2000).

Conversely, neuropsychological observations have the potential to dissociate cognitive processes and their critical neural substrates. For instance, evidence of separate and dissociable routes to access semantic information about people has come from patients with prosopagnosia. Such patients might fail to recognize familiar faces while still being able to identify the corresponding voices (Tranel *et al.*, 1988; De Renzi *et al.*, 1991), or vice versa (Luzzi *et al.*, 2017). Similarly, a loss of person-specific knowledge, regardless of stimulus modality, can be accompanied by intact visual processing faculties and above-chance performance on forced-choice

familiarity tasks (Hanley *et al.*, 1989). Finally, some studies have described patients with selective impairment of proper name retrieval from face stimuli (Mckenna & Warrington, 1980; Lucchelli & De Renzi, 1992). However, while lesions of posterior face network are more common, those affecting the ATL are rare, limiting our ability to discern the role of the entire network on the basis of stroke. Evidence from patients who underwent anterior temporal lobe resection due to drug-resistant epilepsy offer some insight (Seidenberg *et al.* 2002; Glosser *et al.*, 2003, Drane *et al.*, 2013). For example, a recent study suggests that the left and right ATL resection are associated with greater relative impairments in famous face naming and recognition, respectively (Rice *et al.*, 2018a). However, inferences are limited by the potential for pre-surgical functional reorganization of temporal lobe function, such that the population might not reflect typical lateralization profiles. Focal neurodegenerative conditions offer a unique opportunity to investigate the neural network underpinning face processing (Hutchings *et al.*, 2017) as different clinical syndromes are associated with fairly circumscribed atrophy affecting, and spreading within, specific anatomical and functional networks (Seeley *et al.*, 2009, Mandelli *et al.*, 2016). For instance, Alzheimer's dementia (AD) patients' performance in face recognition tasks illustrates the dissociation between discriminating unknown and familiar faces predicted by cognitive models such as that of Bruce and Young (Wilson *et al.*, 1982; Della Salla, 1995). A recent literature review detected disruptions to the face processing network in virtually all frontotemporal dementia (FTD) subtypes, highlighting that specific symptomatology depends on the neuroanatomical region affected by the disease (Hutchings *et al.*, 2017). In some conditions, atrophy is limited to regions of the extended face network (i.e., ATL, amygdala, insula, frontal lobe and the limbic system), while in others it involves areas of the core system as well (e.g. superior temporal sulcus, lateral occipital cortex). The comparison of patients' behavioral symptoms, while confirming that the core system is

involved in both low-level and higher-order conceptual processing, suggests a dynamic bidirectional interaction, where a breakdown in one system can affect the other (Hutchings *et al.*, 2017). Moreover, these conditions differentially impact upon the left and right hemispheres. For example, the semantic variant of primary progressive aphasia (svPPA, or semantic dementia) can present with either left-predominant or right-predominant ATL atrophy (Edwards-Lee *et al.*, 1997, Seeley *et al.*, 2005, Chan *et al.*, 2009). Comparisons of these two presentations have associated atrophy of the left ATL with greater face naming impairments, and the right ATL with greater face recognition impairments (Evans *et al.*, 1995; Gentileschi *et al.*, 2001; Gainotti *et al.*, 2003; Gorno-Tempini *et al.*, 2004; Thompson *et al.*, 2004; Gefen *et al.*, 2013). Indeed, greater impairments in visual tasks more generally appear as a key feature of predominantly right ATL atrophy, while more severe deficits in verbal tasks are observed in cases with predominantly left atrophy (Snowden *et al.*, 2012; Binney *et al.*, 2016; Woollams and Patterson, 2017, Snowden *et al.*, 2017). These observations have been instrumental in developing models of the semantic system where the ATL acts as a transmodal hub, primarily operating bilaterally but with crucial asymmetries (Lambon-Ralph *et al.*, 2017). Finally, evidence from non-invasive brain stimulation technique such as transcranial magnetic stimulation (TMS) complements the neuropsychological findings. By creating virtual, temporary, lesions of the ATLs, these studies suggest that both temporal poles play a pivotal role in semantic processing of both pictures and words (Pobric *et al.*, 2010), with naming being particularly impaired by stimulation of the left hemisphere (Woollams *et al.*, 2017).

In summary, converging evidence from neuropsychological and neuroimaging findings indicates that 1) perception takes place primarily in the right fusiform gyrus (Kanwisher *et al.*, 1997; Gorno-Tempini *et al.*, 1998), 2) multimodal person-specific semantic information is stored in the anterior/lateral temporal lobe, possibly bilaterally (Gorno-Tempini and Price, 2001;

Brambati *et al.*, 2010; Gefen *et al.*, 2013), and likely 3) naming involves the left anterior temporal lobe (Gefen *et al.*, 2013) while familiarity checking the right one (Gainotti 2007).

In the present study, we sought to identify the cognitive and neuroanatomical substrates involved in the different stages of famous faces processing. We capitalized on the variability offered by our cohort of neurodegenerative patients in terms of both brain atrophy site and cognitive profiles. A large, heterogeneous set of volunteers, including patients and healthy controls, underwent neuropsychological testing as well as structural imaging data acquisition. Cortical volumetric data was correlated with participants' performance in three tasks that examined familiarity judgment, semantic association, and naming of famous faces. In line with previous neuropsychological evidence (Gainotti 2007), we predicted that naming and semantic association task performance would correlate with the left anterior temporal gray matter volume while performance in familiarity judgements would correlate with the right ATL.

Materials and Methods

Participants

We selected all subjects from the University of California, San Francisco's Memory and Aging Center (UCSF MAC) who underwent the UCSF Famous Face Recognition Battery (Gorno-Tempini and Price, 2001, Gorno-Tempini, Rankin, *et al.*, 2004) between 2002 and 2014. These included 18 healthy normal controls (NCs) and 105 patients whose diagnosis fell in one of three clinical spectra, for a total of 123 participants (the map of atrophy over all participants can be appreciated in Suppl. Fig. 1). Twenty participants met criteria for Alzheimer's disease (AD) or

Mild Cognitive Impairment (MCI) (McKhann *et al.*, 1984) (hereafter: AD spectrum). Twenty-five participants met criteria for behavioral variant frontotemporal dementia (bvFTD) (Rascovsky *et al.*, 2011), Corticobasal Degeneration (CBD), or Progressive Supranuclear Palsy (PSP) (Boxer *et al.*, 2006) (hereafter: FTD spectrum). Finally, sixty participants met criteria for PPA (Gorno-Tempini *et al.*, 2011), 43 of whom were classified as svPPA, 7 as lvPPA and 10 as nvPPA. The consensus diagnoses were based on the clinical findings and the neuropsychological profile obtained through neuropsychological screening and speech and language assessment administered to all participants (see below). The eighteen older normal controls (NC) were recruited from the University of California San Francisco Memory and Aging Center healthy aging cohort, a collection of participants with normal cognitive and neurological exam and MRI scans without clinically evident strokes. Inclusion criteria required the absence of any psychiatric symptoms or cognitive deficits (i.e., Clinical Dementia Rating - CDR = 0, Mini- Mental State Examination - MMSE $\geq 28/30$, and verbal and visuospatial delayed memory performance \geq the 25th percentile). We included patients from different diagnostic groups as well as NCs for two main reasons. First, greater variance in neuropsychological testing scores and grey matter volume increases the statistical power to detect brain-behavior relationships across the whole brain. Second, inclusion of NCs ensures that the normal end of the regression line is represented in all analyses, regardless of the brain region or behavior in question. Each participant signed informed consent documents in accordance with the Declaration of Helsinki and the study was approved by the UCSF Committee for Human Research.

Neuropsychological evaluation

Screening battery

All subjects underwent neuropsychological testing with a comprehensive battery of language, memory, visuospatial, executive functions, and behavior that has been described extensively in Kramer *et al.*, 2003.

[please insert Fig. 1 here]

Famous faces processing tasks

Famous face processing was assessed using an experimental battery, the UCSF Famous Faces Battery, which comprises three different tasks. The first one, Famous Face Confrontation Naming, prompts subjects to name sequentially presented headshots of celebrities (Fig. 1a). Thus, successfully perform this task requires both access to the PIN and retrieval of the proper name. In the second one, Famous Face Semantic Association, subjects are instructed to match two famous faces – among three choices - according to their profession. In each trial, the three famous faces are carefully matched for perceptual characteristics and facial expression (Fig. 1b). This ensures that inferences based on perceptual similarity alone would not be sufficient to differentiate between the targets and the distractor. Instead, identification of the celebrities and retrieval of semantic/biographical details is necessary to perform the task correctly. Hence, this task requires access to the PIN, yet not necessarily the retrieval of the proper name. Finally, in the Famous Face Familiarity Judgment task, subjects perform a forced choice task between four faces in which only one is famous. In this task, retrieval of proper name or of semantic/biographical details is not required: it can be performed even if access to the PIN is compromised, as long as familiarity units are preserved. Faces are framed with a black oval mask to avoid any possible cueing effects from pictures' background (Fig. 1c). Each task includes 20 trials. The famous faces came from a pool

of 200 black-and-white photographs of celebrities in different professional categories whose familiarity was determined by a behavioral study previously described in Gorno-Tempini and Price, 2001. The non-famous faces were matched to the famous ones for mean age, sex and facial expression. All faces were matched for mean luminance. It should be noted that, inevitably, the chance level is not equated across tasks, in particular, it is 20% for the Famous Face Familiarity Judgment task (i.e., detect a target vs. three foils) and 50% for Famous Face Semantic Association (i.e., detect a target vs. one foils).

[please insert Table 1 here]

Statistical analysis

Demographic characteristics, as well as cognitive, speech and language performance were examined using the Shapiro-Wilk test for normality. The Kruskal-Wallis non-parametric test was used to determine overall group differences. Statistical significance was examined based on 0.05 significance level. These analyses were executed using SPSS 20.0 software and R program for Scientific Computing.

[please insert Fig 2 here]

Neuroimaging

MRI acquisition

T1 images were acquired for all subjects with sequences, previously described, on either 1.5T (n=87, Gorno-Tempini *et al.*, 2004), 3T (n= 20, Mandelli *et al.*, 2014), or 4T (n= 16, Tosun

et al., 2013) systems equipped with a standard quadrature head coil. MRI scans were acquired within 1 year of each visit and in each case the first available image was used for analysis.

Voxel Based Morphometry (VBM)

T1-weighted images processing and statistical analyses were performed using the VBM8 Toolbox implemented in Statistical Parametric Mapping (SPM8, Wellcome Trust Center for Neuroimaging, London, UK, <http://www.fil.ion.ucl.ac.uk/spm>) running under Matlab R2013a (MathWorks). The images were segmented into grey matter, white matter, and CSF based on an adaptive maximum posterior technique (Rajapakse *et al.*, 1997) that takes into account intensity inhomogeneity and other local variations of intensity. This segmentation approach also uses partial volume estimation with a simplified mixed model of two tissue types (Rajapakse *et al.*, 1997). The images were then registered to the Montreal Neurological Institute (MNI) space through an affine and a non-linear deformation. The non-linear deformation parameters were calculated with the high dimensional diffeomorphic anatomical registration through exponentiated lie algorithm and the predefined templates with the diffeomorphic anatomical registration through exponentiated lie toolbox (DARTEL, Ashburner, 2007). The images were modulated by multiplying the voxel values by the Jacobian determinant derived from the spatial normalization to ensure that relative volumes of grey matter were preserved. Finally, the images were smoothed with a full-width at half-maximum (FWHM) Gaussian kernel filter of 10 x10 x10 mm in order to make the data more normally distributed and to compensate for inexact spatial normalization. Data were then analyzed with a multiple regression model entering famous faces naming, semantic association, and familiarity judgment scores as covariates of interest. Additional covariates of no interest included age, gender, handedness, MR scanner field strength, and total intracranial volume (TIV). All

participants were entered as a single group, an approach successfully adopted by previous studies looking at voxelwise brain-behavior correlations (Amici et al., 2007, Henry et al., 2016, Shdo et al., 2018). Three contrasts were set to examine GM volume association with naming ([1 0 0] t-contrast), semantic retrieval ([0 1 0] t-contrast), and familiarity judgment ([0 0 1] t-contrast) performance. Whole-brain statistical maps were first examined at voxel-wise significance level of $p < .001$ uncorrected. Correction for multiple comparisons was then performed by controlling the family-wise error (FWE) rate at $P < 0.05$ at the cluster level.

[please insert Table 2 here]

Results

Behavioral results

Demographics and Screening Battery

The results of the screening battery, as well as demographic information, are reported in Table 1. CDR total score and MMSE did not differ between patient groups aside from differences between diagnostic categories from normal controls. Among the PPA variants, the lvPPA were slightly younger and had longer disease duration although they were not significantly different from the other groups. SvPPA demonstrated significantly worse performance in language testing on the Abbreviated Boston Naming Test and Peabody Picture Vocabulary Test. No differences were seen among the groups on the visuospatial tests or the Benton Face Recognition or Face Matching. In language testing, lvPPA demonstrated significantly worse performance on syntax comprehension and repetition while nfvPPA demonstrated significantly worse performance on lexical fluency.

[please insert Fig 3 here]

UCSF Famous Faces Battery

Patients classified as svPPA showed the worst performance, with significantly lower scores than nfvPPA on all three tasks and lower scores than lvPPA on the famous faces naming task. Moreover, lvPPA patients showed worse performances on the famous faces naming and semantic association tasks as compared to nfvPPA (Fig 2 and Table 1).

[please insert Fig 4 here]

Imaging results

Subjects' scores on the famous faces naming task correlated with grey matter volume in the left temporal pole and left superior, middle, and inferior temporal gyri (Fig. 3 and Table 2). Furthermore, an additional cluster is observed on the right ATL. Similarly, scores on the famous faces semantic association task correlated with grey matter volume in the left temporal pole, as well as left middle and inferior temporal gyri (Fig 4 and Table 2).

[please insert Fig 5 here]

In sharp contrast, famous faces familiarity judgment scores correlated with grey matter volume in the right middle temporal gyrus (Fig 5 and Table 2).

[please insert Fig 6 here]

Post hoc analysis

Observing such a striking functional distinction between the left and the right hemisphere, and considering the known clinical distinction between left and right temporal variant of svPPA, a supplementary analysis focused on the svPPA patients in our sample. In particular, we sought to address two possible interpretation of our results: (1) that the results are driven by svPPA patients alone, and (2) that the lateralization of familiarity to the right hemisphere is driven by the most severe among our svPPA patients. First, it could be argued that svPPA patients alone, exhibiting the most severe ATL atrophy (Suppl. Fig. 2), are driving the results. To confute this hypothesis we tested whether the observed correlations between ATL volume and behavioral scores would survive once svPPA patients are removed from the analyses. This analysis confirmed the significant correlation of left ATL volume with naming ($R^2 = 0.33$, $p < 0.001$) and semantic association ($R^2 = 0.21$, $p < 0.001$), as well as the significant correlation of right ATL volume with familiarity ($R^2 = 0.28$, $p < 0.001$) (Suppl. Fig. 3). Second, one could hypothesize that advanced cases with bilateral atrophy would be affected in both naming and familiarity judgment: the more widespread the atrophy, the more severe the cognitive impairment. A distinction between right ($n=15$) and left ($n=28$) svPPA was made by consensus diagnosis of the Language Neurobiology Laboratory at UCSF based on overall clinical profile (Seeley et al., 2005). Overall, left-sided svPPA demonstrated significantly worse scores in animal fluency, Abbreviated Boston Naming Test, and Peabody Picture Vocabulary Test. With respect to the UCSF Famous Faces Battery, no differences were seen between these two groups in performance on the famous faces naming or semantic association tasks, while right-sided svPPA showed worse performances on the famous faces familiarity judgment (Supp. Table 1). These results suggest that in our sample, left svPPA patients were slightly more severe than right svPPA, with the latter only showing marked

impairment in famous faces familiarity judgment. As a matter of fact, the key difference between the two groups appeared to be the relationship between their overall naming performance (as measured with Boston Naming task) and the famous faces familiarity judgment (Suppl. Fig. 4). Contrary to right svPPA patients, left svPPA ones, even if profoundly impaired in naming, scored fairly well in the famous faces familiarity judgment task due to the (relatively) spared right ATL.

Discussion

In the present study, we isolate the cognitive and neural substrates of three stages of the famous faces processing cascade (i.e., naming, semantic processing, and familiarity judgment) in a large cohort of neurodegenerative patients. We linked naming to the left ATL extending to MTG; semantic/biographical information retrieval to the left ATL, extending posteriorly and ventrally in the ITG; and familiarity processing to the right anterior middle temporal gyrus.

Famous faces are complex, semantically and lexically relevant, visual stimuli that trigger crucial cognitive functions at the intersection of perceptual, semantic and lexical processes. Hence, the results of our study significantly contribute to the understanding of the neuroanatomical correlates of such systems, with important theoretical and clinical implications as discussed below.

Famous face processing: from knowing to naming

Neurocognitive models of famous face analysis were built on behavioral evidence, in healthy subjects, of failures at different levels of processing: judgment on familiarity (e.g., *this is a young white man, but I don't know if he is a famous or not*), retrieval of semantic information (e.g., *I know this face, but I don't know who he is*), and finally naming (e.g., *he is the president*

who was shot in Dallas, but I cannot remember his name). The cognitive tasks we designed allow the evaluation of each of these three phenomena in patients with neurodegenerative disorders.

None of our participant groups demonstrated specific deficits in visuospatial analysis of unfamiliar faces (see Table 1). This is particularly true for patients with svPPA who have severe difficulties in semantic processing and proper name retrieval of famous faces, but do not have the classical syndrome of visual prosopagnosia and are not able to retrieve biographical information even when presented with proper names (e.g., Snowden *et al.*, 2004). Instead, we observed different degrees of impairments in naming, semantic/biographical attributes retrieval, and familiarity feeling across clinical spectra. Crucially, we detect significant associations between scores on familiarity judgments and right temporal volume loss, and between performance on famous face semantic processing and naming with left temporal volume loss. It should be noted that the detection of a small cluster correlating naming with right ATL is expected given that the neurodegenerative diseases included in the study show highly asymmetrical patterns of atrophy, yet are intrinsically bilateral in nature.

Our findings provide empirical evidence of the cognitive and neuroanatomical decoupling between the classically described familiarity and identification units (Bruce and Young, 1986). Moreover, our results support a model in which the concerted functionality of both hemispheres is required for the successful identification of famous people. In right svPPA patients, damage to the right ATL is associated with deficits in all tasks. These patients explicitly complain of face recognition deficits, likely because they cannot compensate their semantic loss with a sense of visual familiarity. Instead, in left svPPA patients poor scores in semantic/biographical knowledge and naming can co-occur with spared feelings of familiarity. This retained sense of familiarity, especially for personally known faces, could be the reason why left svPPA patients usually do not

complain of people identification or face recognition deficits despite their severely impaired performance on formal testing. The right ATL would thus function as key interface between purely visual processing in fusiform regions and retrieval of verbally-based biographical and lexical information in the left ATL.

We could speculate that the familiarity feelings automatically generated in the right ATL enable (or at least facilitate, as already elaborated in Gainotti 2007) downstream processes such as person-specific information retrieval. A parallel could then be drawn between telling real words vs. pseudowords (the first step towards meaning access) and familiar vs. unfamiliar faces (the first step towards identifying people). The first one appears to be a function of the left temporal lobe (Binney *et al.*, 2016), while the second one would be its right hemisphere counterpart. This type of visual semantic information is critical for rapid social/emotional processing and might have evolved together, as further discussed below.

Taking sides on the semantic system

Our results of a distributed bilateral ATL network for the identification of famous people provide evidence for the overall organization of the semantic system.

The most influential models on the neural substrate of semantic memory acknowledge the need for peripheral, modality specific nodes, as well as multimodal convergence zones supporting merging and binding of information into conceptual representations independent of input modality (Lambon-Ralph *et al.*, 2017, Borghesani *and* Piazza, 2017). It is also well-described how concepts are composed of many features (e.g., prototypical shape, color, function, location), whose salience varies across different domains. For example, visual/sensory features are critical for the identification of animals and emotions (e.g., *a big striped cat-like animal is a dangerous predator*),

while action affordances are most important for manipulable tools (e.g., *anything with a blade can be used to cut*) (Cree and McRae, 2003). The relative weight of each feature is further modulated by the task at hand, and the identification of people is a special case: it requires high-level visual perception and intra-category identification of one specific exemplar among millions. Moreover, it is a link to highly verbal, encyclopedic knowledge, and promotes the retrieval of a *pure referring expression* (the proper name) not shared by any other item (Wittgenstein, 1953). Famous faces are thus the ideal stimuli to study non-verbal access to semantic and lexical knowledge. As already highlighted by Snowden and colleagues (2004), with famous faces researchers can rule out any effect of perceptual affordance, as the links between face, name, and semantic attributes are arbitrary. With other visual stimuli (e.g., the picture of a pitcher), the perceptual information would be intrinsically linked with its functional meaning (e.g., being handled and poured). Moreover, famous faces allow to reliably isolate the sense of familiarity, the elusive feeling of knowing, an operation virtually impossible with other visual stimuli such as tools or animals.

Neuropsychological data stemming from studies of svPPA patients, indicate the ATLs as the most important hub for semantic processing (Hodges *et al.*, 1992). The crucial role of the ATL has now been widely accepted thanks to converging evidence from other neurological disorders, such as stroke, herpes simplex virus encephalitis, and epilepsy (Noppeney *et al.*, 2007, Schwartz *et al.*, 2009, Rice *et al.*, 2015, Rice *et al.*, 2018a, Rice *et al.*, 2018b). However, the relative role of the right vs. left ATL is still highly debated. Crucial findings come from svPPA cases, where early diagnosis is allowing the study of more selective (predominantly) left vs. right ATL atrophy. Overall, the typical clinical presentation of right svPPA patients is characterized by behavioral symptoms (e.g., cold interpersonal behavior, loss of empathy) and difficulty with person identification and semantic knowledge for persons (Thompson *et al.*, 2003, Gorno-Tempini *et al.*,

2004; Snowden *et al.*, 2012), with less severe naming deficits and surface dyslexia compared to left svPPA cases (Binney *et al.*, 2016). Consequently, the left temporal lobe has been associated with processing of words and objects (Hodges *et al.*, 1992; Mummery *et al.*, 2000), while the right appears to be associated with processing of socio-emotional stimuli (Rankin *et al.*, 2006; Zahn *et al.*, 2009, 2017). Given the known interplay between handedness and lateralization of domain specific areas (Willems *et al.*, 2009), the picture is further complicated by the evidence of increased non-right-handedness in svPPA population (Miller *et al.*, 2013).

Overall, three main hypotheses have been put forward to explain the representational differences between left and right ATL, that focus, respectively, on the type of input (verbal vs pictorial stimuli), the content of the representation (charged with socio-emotional implications or not), and the format of the representation (language mediated vs sensory-motor) (Gainotti, 2015). Our finding of a difference between right ATL damage (associated with deficits in familiarity judgments) and left ATL damage (associated with deficits in naming and semantic/biographical information retrieval), provides empirical support for those perspectives that highlight differential functional specialization of the left and right ATL based on type of semantic features and task (Gainotti, 2015, Lambon-Ralph *et al.*, 2017). It is worth noticing that, thanks to the highly-controlled stimuli we adopted, neither semantic/biographical information retrieval nor familiarity judgments could rely on low level perceptual features. Face triplets were matched for general appearance, thus requiring not only perceptual recognition but also retrieval of specific verbally-based biographical information, while the forced-choice familiarity judgment only required a feeling of visual familiarity. Most of our left svPPA patients reported “guessing” who was the famous one among the 4 similarly looking faces (see Fig. 1). The observed divergence cannot be ascribed to input modality differences as the same pictorial stimuli were used across the three

tasks. Hence, the difference can only derive from distinct representational formats (i.e., familiarity feelings do not require a verbal, language-mediated code, Gainotti, 2012), or be due to the content of the representation (i.e., familiarity feelings have tighter ties with emotions and social aspects than information on occupation and name, Olson *et al.*, 2007). It should be noted that these views are not incompatible and should rather be seen as complementary: many socio-emotional aspects of semantic knowledge cannot be easily represented with a language-mediated code (Gainotti, 2015).

The role played by the right ATL in facial familiarity processing calls for further investigations into the relation between familiarity and frequency, as well as between familiarity and socio-affective processing. Famous faces could be conceived as low frequency unique entities on the same continuum as objects. To test if and how stimuli category (e.g., celebrities vs. landmarks) interacts with task requests (e.g., naming vs. recognizing), future empirical work should aim to compare unique entities belonging to different semantic categories, while controlling for the frequency in which participants encounter them (Gainotti 2007, Montembeault *et al.* 2017, Rice *et al.*, 2018c). Additionally, it has been suggested that the right temporal lobe binds sensory representations recruited for social and emotional processes due to its connections with the limbic system (Olson *et al.*, 2007; Oishi *et al.*, 2015). This would explain the combination of deficits in person identification and impairments in social and behavioral domains observed in patients with damage to the right temporal atrophy, including bvFTD and right variant of svPPA (Kumfor *and* Piguet, 2012, Rankin *et al.*, 2006; Zahn *et al.*, 2009, 2017). Recognizing a face as familiar has cognitive implications (promoting retrieval of person-specific information), as well as behavioral ramification (allowing selection of the appropriate course of action) and emotional consequences (impacting social interaction and personal feelings). Therefore, a second line of research would

investigate possible correlations between patients' performance in familiarity judgment tasks and measures of social cognition, such as emotional face comprehension (Rosen *et al.*, 2002). These kind of data will be instrumental in testing models that associate the right hemisphere with non-verbal, automatic, primitive, emotional processing heavily relying on sensorimotor functions, in contrast with the verbal, conscious and intentional, phylogenetically younger, cognitive processing anchored in the left hemisphere (Gainotti, 2018).

Clinical implications

Our results have one main clinical implication: deficits in semantic tasks that do not require verbal processing could indicate a predominantly right ATL damage. To date, notwithstanding the growing number of descriptions of right svPPA cases (e.g., Edwards-Lee *et al.*, 1997; Gorno-Tempini *et al.*, 2004; Joubert *et al.*, 2006), there are no established diagnostic criteria to help differential diagnosis. Patients with right ATL atrophy are inconsistently diagnosed either as svPPA - when they reach clinical attention lamenting word-finding or object recognition problems, or bvFTD - when loss of empathy and deficits in emotion recognition are first noticed. Although individual variation exists within each subgroup (Woollams *and* Patterson, 2017), dissociations in neuropsychological performance between predominantly right and predominantly left svPPA patients have been consistently reported, especially when examining not only the overall accuracy but also the type of error committed (Snowden *et al.*, 2017). However, left and right variants of svPPA progress into similar clinical profiles as atrophy spreads (Seeley *et al.*, 2005; Brambati *et al.*, 2009; Kumfor *et al.*, 2016), thus only cases detected early enough can be easily distinguished. Crucially, right svPPA patients often present with behavioral traits such as rigidity and apathy, which are routinely detected in bvFTD patients. It should be noted that the overwhelming majority

of svPPA cases (83%) is associated with FTLD-TDP type C pathology (Spinelli et al., 2017), while bvFTD cases present more variability across FTLD subtypes (Perry *et al.*, 2017). Identification of right svPPA patients has thus significant relevance in the prediction of the underlying pathology, a pivotal step as pharmacological interventions become available. Our results suggest that, in order to help the detection of predominantly right ATL pathology in early stages of the disease, deficits in non-verbally mediated semantic knowledge should be carefully noted. To this end, specific tests should be conceived enabling the dissociation of semantic representations in terms of both content and format (e.g., verbally-mediated vs. sensory-based).

Limitations

The main limitation of the present investigation is the relatively small -and unbalanced across clinical spectra- number of patients, a consequence of the rareness of these diseases. Converging evidence from fMRI and TMS studies will help ruling out potential confounding factors that cannot be fully addressed when comparing these rare cases (e.g., disease severity and duration). We carefully design the three tasks to allow separate assesment of key processing steps and selected the stimuli as to avoid perceptual confunds. However, only non-verbal, visual inputs were used (i.e., famous people faces). Hence, the results cannot be generalized to famous person identification as achieved through other sensory modalities (Gainotti, 2015). Future studies shall aim to integrate non-verbal auditory inputs (i.e., famous people voices), while comparing performance across tasks explicitly addressing different cognitive processes, as done here. This will be instrumental in understanding the interaction between input format (auditory vs. visual) and cognitive process (e.g., familiarity judgment vs. semantic retrieval).

Concluding remarks

This study showed that different stages of famous faces processing rely on distinct neural substrate in the right (familiarity judgment) and left (semantic/biographical information retrieval and naming) anterior temporal lobe. These findings reconcile theories on the lateralization of face processing and on the neural correlates of semantic knowledge. Finally, we offer that these observations will be instrumental in refining the distinction between left and right variant of temporal degeneration.

Acknowledgements

The study was supported by grants NINDS R01 NS050915, NIA P50 AG023501, NIA P01 AG019724, NIDCD K24 DC015544, NIA U01 AG052943, NIA R01 AG038791, U54 NS092089, NIA U01 AG045390. Additional funds include the Larry Hillblom Foundation and the Global Brain Health Institute. These supporting sources had no involvement in the study design, collection, analysis or interpretation of data, nor were they involved in writing the paper or the decision to submit this report for publication. The authors thank the patients and their families for the time and effort they dedicated to the research.

Conflicts of interest

None to be declared.

References

- Amici, S., Brambati, S. M., Wilkins, D. P., Ogar, J., Dronkers, N. L., Miller, B. L., & Gorno-Tempini, M. L. (2007). Anatomical correlates of sentence comprehension and verbal working memory in neurodegenerative disease. *Journal of Neuroscience*, 27(23), 6282-6290.
- Ashburner J. A fast diffeomorphic image registration algorithm. *Neuroimage* 2007; 38: 95–113.
- Binney RJ, Henry ML, Babiak M, Pressman PS, Santos-Santos MA, Narvid J, et al. Reading words and other people: A comparison of exception word, familiar face and affect processing in the left and right temporal variants of primary progressive aphasia. *Cortex* 2016; 82: 147–163.
- Blank H, Wieland N, von Kriegstein K. Person recognition and the brain: Merging evidence from patients and healthy individuals [Internet]. *Neurosci. Biobehav. Rev.* 2014; 47: 717–734.
- Borghesani V, Piazza. The neuro-cognitive representations of symbols: the case of concrete words. *Neuropsychologia* 2017
- Boxer AL, Geschwind, Michael D, Nataliya B, Gorno-Tempini ML, Schauer GF, Miller BL, et al. Patterns of Brain Atrophy That Differentiate Corticobasal Degeneration Syndrome From Progressive Supranuclear Palsy. 2006; 63
- Brambati SM, Benoit S, Monetta L, Belleville S, Joubert S. The role of the left anterior temporal lobe in the semantic processing of famous faces [Internet]. *Neuroimage* 2010; 53: 674–681.
- Brambati SM, Rankin KP, Narvid J, Seeley WW, Dean D, Rosen HJ, et al. Atrophy

progression in semantic dementia with asymmetric temporal involvement: A tensor-based morphometry study. *Neurobiol. Aging* 2009; 30: 103–111.

Bruce V, Young A. Understanding face recognition. *Br. J. Psychol.* 1986; 77: 305–327.

Butler, C. R., Brambati, S. M., Miller, B. L., & Gorno-Tempini, M. L. The neural correlates of verbal and non-verbal semantic processing deficits in neurodegenerative disease. *Cognitive and behavioral neurology: official journal of the Society for Behavioral and Cognitive Neurology*, 2009, 22(2), 73.

Chan D, Anderson V, Pijnenburg Y, Whitwell J, Barnes J, Scahill R, et al. The clinical profile of right temporal lobe atrophy. *Brain* 2009; 132: 1287–1298.

Cree, G. S., & McRae, K. (2003). Analyzing the factors underlying the structure and computation of the meaning of chipmunk, cherry, chisel, cheese, and cello (and many other such concrete nouns). *Journal of Experimental Psychology: General*, 132(2), 163.

Collins JA, Olson IR. Beyond the FFA: The Role of the Ventral Anterior Temporal Lobes in Face Processing. 2015: 65–79.

Della Salla S. Cognitive modelling of face processing: evidence for dementia of the Alzheimer type. *Neuropsychologia* 1995; 33: 189–198.

De Renzi E, Faglioni P, Grossi D, Nichelli P. Apperceptive and Associative Forms of Prosopagnosia [Internet]. *Cortex* 1991; 27: 213–221.

Drane, D.L., Ojemann, J.G., Phatak, V., Loring, D.W., Gross, R.E., Hebb, A.O., Silbergeld, D.L., Miller, J.W., Voets, N.L., Saindane, A.M. and Barsalou, L., (2013). Famous face identification in temporal lobe epilepsy: support for a multimodal integration model of semantic memory. *Cortex*, 49(6), pp.1648-1667.

Edwards-Lee, T., Miller, B. L., Benson, D. F., Cummings, J. L., Russell, G. L., Boone, K.,

& Mena, I. (1997). The temporal variant of frontotemporal dementia. *Brain: a journal of neurology*, 120(6), 1027-1040.

Ellis HD, Jones DM, Mosdell N. Intra- and inter-modal repetition priming of familiar faces and voices. [Internet]. *Br. J. Psychol.* 1997; 88 (Pt 1): 143–56.

Evans JJ, Higgs AJ, Antoun N, Hodges JR. Progressive prosopagnosia associated with selective right temporal lobe atrophy. A new syndrome? *Brain* 1995; 118: 1–13.

Gainotti, G. (2007) Different patterns of famous people recognition disorders in patients with right and left anterior temporal lesions: a systematic review. *Neuropsychologia* 45(8): 1591-1607.

Gainotti, G. (2007). Face familiarity feelings, the right temporal lobe and the possible underlying neural mechanisms. *Brain research reviews*, 56(1), 214-235.

Gainotti, G. (2012) The format of conceptual representations disrupted in semantic dementia: a position paper. *Cortex*, 48(5), 521-529.

Gainotti, G., (2015). Is the difference between right and left ATLs due to the distinction between general and social cognition or between verbal and non-verbal representations?. *Neuroscience & Biobehavioral Reviews*, 51, pp.296-312.

Gainotti, G. (2015). Implications of recent findings for current cognitive models of familiar people recognition. *Neuropsychologia*, 77, 279-287.

Gainotti, G., (2018). Emotions and the Right Hemisphere: Can New Data Clarify Old Models?. *The Neuroscientist*

Gainotti G, Barbier A, Marra C. Slowly progressive defect in recognition of familiar people in a patient with right anterior temporal atrophy. *Brain* 2003; 126: 792–803.

Gefen T, Wieneke C, Mardersteck A, Whitney K. Naming vs knowing faces in primary

progressive aphasia A tale of 2 hemispheres. *Neurology* 2013; 658–664.

Gentileschi V, Sperber S, Spinnler H. Crossmodal Agnosia for Familiar People As a Consequence of Right Infero Polar Temporal Atrophy [Internet]. *Cogn. Neuropsychol.* 2001; 18: 439–463.

Glosser, G., Salvucci, A.E. and Chiaravalloti, N.D., 2003. Naming and recognizing famous faces in temporal lobe epilepsy. *Neurology*, 61(1), pp.81-86.

Gobbini MI, Haxby J V. Neural systems for recognition of familiar faces. *Neuropsychologia* 2007; 45: 32–41.

Gorno-Tempini M., Hillis AE, Weintraub S, Kertesz A, Mendez M, Cappa SF, et al. Classification of primary progressive aphasia and its variants. 2011; 2: 1–10.

Gorno-Tempini M, Dronkers NF, Rankin KP, Ogar JM, Phengrasamy L, Rosen HJ, et al. Cognition and anatomy in three variants of primary progressive aphasia. [Internet]. *Ann. Neurol.* 2004; 55: 335–346.

Gorno-Tempini M, Rankin K, Woolley J, Rosen H, Phengrasamy L, Miller B. Cognitive and behavioral profile in a case of right anterior temporal lobe neurodegeneration. *Cortex* 2004; 40: 631–644.

Gorno-Tempini ML, Price CJ. Identification of famous faces and buildings A functional neuroimaging study of semantically unique items. *Brain* 2001; 124: 2087–2097.

Gorno-Tempini ML, Price CJ, Josephs O, Vandenberghe R, Cappa SF, Kapur N, et al. The neural systems sustaining face and proper- name processing. *Brain* 1998; 121: 2103–2118.

Hanley JR, Young AW, Pearson NA. Defective recognition of familiar people. *Cogn Neuropsychol* 1989; 6: 179–210.

Haxby J V, Hoffman E a, Gobbini MI. The distributed human neural system for face

perception [Record Supplied By Publisher]. Trends Cogn Sci 2000; 4: 223–233.

Henry, M. L., Wilson, S. M., Babiak, M. C., Mandelli, M. L., Beeson, P. M., Miller, Z. A., & Gorno-Tempini, M. L. (2016). Phonological processing in primary progressive aphasia. *Journal of cognitive neuroscience*, 28(2), 210-222.

Hodges, J. R., & Graham, K. S. (1998). A reversal of the temporal gradient for famous person knowledge in semantic dementia: Implications for the neural organisation of long-term memory. *Neuropsychologia*, 36(8), 803-825.

Hodges JR, Patterson K, Oxbury S, Funnell E. Semantic dementia. Progressive fluent aphasia with temporal lobe atrophy. *Brain* 1992; 115: 1783–1806.

Hutchings R, Palermo R, Piguet O, Kumfor F. Disrupted Face Processing in Frontotemporal Dementia: A Review of the Clinical and Neuroanatomical Evidence [Internet]. *Neuropsychol. Rev.* 2017; 27: 18–30.

Joubert S, Felician O, Barbeau E, Ranjeva J-P, Christophe M, Didic M, et al. The right temporal lobe variant of frontotemporal dementia [Internet]. *J. Neurol.* 2006; 253: 1447–1458.

Kanwisher N, McDermott J, Chun MM. The fusiform face area: a module in human extrastriate cortex specialized for face perception. [Internet]. *J. Neurosci.* 1997; 17: 4302–11.

Kramer, J.H., Jurik, J., Sha, S.J., Rankin, K.P., Rosen, H.J., Johnson, J.K., & Miller, B.L. (2003). Distinctive neuropsychological patterns in frontotemporal dementia, semantic dementia, and Alzheimer disease. *Cognitive and Behavioral Neurology*, 16(4), 211–218.

Kriegeskorte, N., Formisano, E., Sorger, B. and Goebel, R., 2007. Individual faces elicit distinct response patterns in human anterior temporal cortex. *Proceedings of the National Academy of Sciences*, 104(51), pp.20600-20605.

Kumfor F, Landin-Romero R, Devenney E, Hutchings R, Grasso R, Hodges JR, et al. On

the right side? A longitudinal study of left- versus right-lateralized semantic dementia [Internet]. Brain 2016; 139: 986–998.

Lambon-Ralph MA, Jefferies E, Patterson K, Rogers TT. The neural and computational bases of semantic cognition [Internet]. Nat. Rev. Neurosci. 2017; 18: 42–55.

Lambon-Ralph MA. and Patterson, K., 2008. Generalization and differentiation in semantic memory. Annals of the New York Academy of Sciences, 1124(1), pp.61-76.

Leveroni CL, Seidenberg M, Mayer AR, Mead L a, Binder JR, Rao SM. Neural Systems Underlying the Recognition of Familiar and Newly Learned Faces. J. Neurosci. 2000; 20: 878–886.

Lucchelli F, De Renzi E. Proper Name Anomia [Internet]. Cortex 1992; 28: 221–230. Available from: [http://dx.doi.org/10.1016/S0010-9452\(13\)80050-0](http://dx.doi.org/10.1016/S0010-9452(13)80050-0)

Luzzi S, Coccia M, Polonara G, Reverberi C, Ceravolo G, Silvestrini M, et al. Selective associative phonagnosia after right anterior temporal stroke [Internet]. Neuropsychologia 2017

Mandelli ML, Vilaplana E, Brown JA, Hubbard HI, Binney RJ, Attygalle S, et al. Healthy brain connectivity predicts atrophy progression in non-fluent variant of primary progressive aphasia. Brain 2016; 139: 2778–2791.

Mckenna P, Warrington EK. Testing for nominal dysphasia. J. Neurol. Neurosurgery, Psychiatry 1980; 43: 781–788.

McKhann G, Drachman D, Folstein M, Katzman R. views & reviews Clinical diagnosis of Alzheimer ' s disease : Neurology 1984; 34: 939.

Mehta S, Inoue K, Rudrauf D, Damasio H, Tranel D, Grabowski T. Segregation of anterior temporal regions critical for retrieving names of unique and nonunique entities reflects underlying long-range connectivity. Cortex 2016; 75: 1–19.

Miller, Z. A., Mandelli, M. L., Rankin, K. P., Henry, M. L., Babiak, M. C., Frazier, D. T., ... & Graff-Radford, N. R. (2013). Handedness and language learning disability differentially distribute in progressive aphasia variants. *Brain*, 136(11), 3461-3473.

Montembeault, M., Brambati, S.M., Joubert, S., Boukadi, M., Chapleau, M., Laforce, R.J., Wilson, M.A., Macoir, J. and Rouleau, I., 2017. Naming unique entities in the semantic variant of primary progressive aphasia and Alzheimer's disease: Towards a better understanding of the semantic impairment. *Neuropsychologia*, 95, pp.11-20.

Mummery CJ, Patterson K, Price CJ, Ashburner J, Frackowiak RS, Hodges JR. A voxel-based morphometry study of semantic dementia: relationship between temporal lobe atrophy and semantic memory 81. *Ann.Neurol.* 2000; 47: 36–45.

Natu V, O'Toole AJ. The neural processing of familiar and unfamiliar faces: A review and synopsis. *Br. J. Psychol.* 2011; 102: 726–747.

Nestor, A., Plaut, D.C. and Behrmann, M., 2011. Unraveling the distributed neural code of facial identity through spatiotemporal pattern analysis. *Proceedings of the National Academy of Sciences*, 108(24), pp.9998-10003.

Noppeney U, Patterson K, Tyler LK, Moss H, Stamatakis EA, Bright P, Mummery C, Price CJ (2007) Temporal lobe lesions and semantic impairment: a comparison of herpes simplex virus encephalitis and semantic dementia. *Brain : a journal of neurology* 130:1138-1147.

Oishi K, Faria A V., Hsu J, Tippet D, Mori S, Hillis AE. Critical role of the right uncinate fasciculus in emotional empathy. *Ann. Neurol.* 2015; 77: 68–74.

Olson IR, Plotzker A, Ezzyat Y. The Enigmatic temporal pole: A review of findings on social and emotional processing. *Brain* 2007; 130: 1718–1731.

Papagno C, Miracapillo C, Casarotti A, Romero Lauro LJ, Castellano A, Falini A, et al.

What is the role of the uncinate fasciculus? Surgical removal and proper name retrieval. *Brain* 2011; 134: 405–414.

Perry, D. C., Brown, J. A., Possin, K. L., Datta, S., Trujillo, A., Radke, A., ... & Gorno-Tempini, M. L. (2017). Clinicopathological correlations in behavioural variant frontotemporal dementia. *Brain*

Pobric, G., Jefferies, E. and Ralph, M.A.L., 2010. Amodal semantic representations depend on both anterior temporal lobes: evidence from repetitive transcranial magnetic stimulation. *Neuropsychologia*, 48(5), pp.1336-1342.

Rajapakse JC, Giedd JN, Rapoport JL. Statistical approach to segmentation of single-channel cerebral MR images [Internet]. *IEEE Trans. Med. Imaging* 1997; 16: 176–186. Available from: <http://ieeexplore.ieee.org/document/563663/>

Rajimehr R, Young JC, Tootell RBH. An anterior temporal face patch in human cortex, predicted by macaque maps [Internet]. *Proc. Natl. Acad. Sci.* 2009; 106: 1995–2000. Available from: <http://www.pnas.org/lookup/doi/10.1073/pnas.0807304106>

Rankin KP, Gorno-Tempini ML, Allison SC, Stanley CM, Glenn S, Weiner MW, et al. Structural anatomy of empathy in neurodegenerative disease. *Brain* 2006; 129: 2945–2956.

Rascovsky K, Hodges JR, Knopman D, Mendez MF, Kramer JH, Neuhaus J, et al. Sensitivity of revised diagnostic criteria for the behavioural variant of frontotemporal dementia. *Brain* 2011; 134: 2456–2477.

Rice GE, Lambon Ralph, M., Hoffman P. (2015) The roles of left versus right anterior temporal lobes in conceptual knowledge: An ALE meta-analysis of 97 functional neuroimaging studies. *Cereb. Cortex*; 25: 4374–4391.

Rice, G.E., Caswell, H., Moore, P., Hoffman, P., Ralph, L. and Matthew, A., (2018a). The

Roles of Left Versus Right Anterior Temporal Lobes in Semantic Memory: A Neuropsychological Comparison of Postsurgical Temporal Lobe Epilepsy Patients. *Cerebral Cortex*, 28(4), pp.1487-1501.

Rice, G.E., Caswell, H., Moore, P., Ralph, L., Matthew, A. and Hoffman, P., (2018b). Revealing the Dynamic Modulations That Underpin a Resilient Neural Network for Semantic Cognition: An fMRI Investigation in Patients With Anterior Temporal Lobe Resection. *Cerebral Cortex*.

Rice, G.E., Hoffman, P., Binney, R.J. and Ralph, M.A.L., (2018c). Concrete versus abstract forms of social concept: an fMRI comparison of knowledge about people versus social terms. *Phil. Trans. R. Soc. B*, 373(1752), p.20170136.

Rosen, H. J., Perry, R. J., Murphy, J., Kramer, J. H., Mychack, P., Schuff, N., ... & Miller, B. L. (2002). Emotion comprehension in the temporal variant of frontotemporal dementia. *Brain*, 125(10), 2286-2295.

Schwartz, M. F., Kimberg, D. Y., Walker, G. M., Faseyitan, O., Brecher, A., Dell, G. S., & Coslett, H. B. (2009). Anterior temporal involvement in semantic word retrieval: voxel-based lesion-symptom mapping evidence from aphasia. *Brain*, 132(12), 3411-3427.

Seeley WW, Bauer AM, Miller BL, Gorno-Tempini ML, Kramer JH, Weiner M, et al. The natural history of temporal variant frontotemporal dementia. *Neurology* 2005; 64: 1384–1390.

Seeley WW, Crawford RK, Zhou J, Miller BL, Greicius MD. Neurodegenerative diseases target large-scale human brain networks. *Neuron* 2009; 62: 42–52.

Seidenberg, M., Griffith, R., Sabsevitz, D., Moran, M., Haltiner, A., Bell, B., Swanson, S., Hammeke, T. and Hermann, B., 2002. Recognition and identification of famous faces in patients with unilateral temporal lobe epilepsy. *Neuropsychologia*, 40(4), pp.446-456.

Shinoura N, Suzuki Y, Tsukada M, Yoshida M, Yamada R, Tabei Y, et al. Deficits in the left inferior longitudinal fasciculus results in impairments in object naming [Internet]. *Neurocase* 2010; 16: 135–139.

Shdo, S. M., Ranasinghe, K. G., Gola, K. A., Mielke, C. J., Sukhanov, P. V., Miller, B. L., & Rankin, K. P. (2018). Deconstructing empathy: neuroanatomical dissociations between affect sharing and prosocial motivation using a patient lesion model. *Neuropsychologia*, 116, 126-135.

Snowden, J. S., Harris, J. M., Thompson, J. C., Kobylecki, C., Jones, M., Richardson, A. M., & Neary, D. (2017). Semantic dementia and the left and right temporal lobes. *Cortex*.

Snowden, J.S., Thompson, J.C. and Neary, D., 2004. Knowledge of famous faces and names in semantic dementia. *Brain*, 127(4), pp.860-872.

Snowden JS, Thompson JC, Neary D. Famous people knowledge and the right and left temporal lobes. *Behav. Neurol.* 2012; 25: 35–44.

Spinelli, E. G., Mandelli, M. L., Miller, Z. A., Santos-Santos, M. A., Wilson, S. M., Agosta, F., ... & Henry, M. L. (2017). Typical and atypical pathology in primary progressive aphasia variants. *Annals of neurology*, 81(3), 430-443.

Thierry, G., & Price, C. J. (2006). Dissociating verbal and nonverbal conceptual processing in the human brain. *Journal of Cognitive Neuroscience*, 18(6), 1018-1028.

Thompson SA, Graham KS, Williams G, Patterson K, Kapur N, Hodges JR. Dissociating person-specific from general semantic knowledge: Roles of the left and right temporal lobes. *Neuropsychologia* 2004; 42: 359–370.

Thompson, S.A., Patterson, K. and Hodges, J.R., 2003. Left/right asymmetry of atrophy in semantic dementia Behavioral–cognitive implications. *Neurology*, 61(9), pp.1196-1203.

Tranel D, Damasio a R, Damasio H. Intact recognition of facial expression, gender, and

age in patients with impaired recognition of face identity. [Internet]. *Neurology* 1988; 38: 690–696.

Tsapkini, K., Frangakis, C. E., & Hillis, A. E. The function of the left anterior temporal pole: evidence from acute stroke and infarct volume. *Brain*, 2011, 134(10), 3094-3105.

Verosky, S.C., Todorov, A. and Turk-Browne, N.B., 2013. Representations of individuals in ventral temporal cortex defined by faces and biographies. *Neuropsychologia*, 51(11), pp.2100-2108.

von der Heide RJ, Skipper LM, Klobusicky E, Olson IR. Dissecting the uncinate fasciculus: Disorders, controversies and a hypothesis. *Brain* 2013; 136: 1692–1707.

Wang Y, Collins JA, Koski J, Nugiel T, Metoki A, Olson IR. Dynamic neural architecture for social knowledge retrieval [Internet]. *Proc. Natl. Acad. Sci.* 2017; 114: E3305–E3314.

Wittgenstein, Ludwig. *Philosophical Investigations*. New York: Macmillan, 1953. Section 79.

Willems, R. M., Peelen, M. V., & Hagoort, P. (2009). Cerebral lateralization of face-selective and body-selective visual areas depends on handedness. *Cerebral Cortex*, 20(7), 1719-1725.

Wilson RS, Kaszniak AW, Bacon LD, Fox JH, Kelly MP. Facial recognition memory in dementia. *Cortex* 1982; 18: 329–336.

Woollams, A. M., & Patterson, K. (2017a). Cognitive consequences of the left-right asymmetry of atrophy in semantic dementia. *Cortex*.

Woollams, A.M., Lindley, L.J., Pobric, G. and Hoffman, P., (2017b). Laterality of anterior temporal lobe repetitive transcranial magnetic stimulation determines the degree of disruption in picture naming. *Brain Structure and Function*, 222(8), pp.3749-3759.

Zahn R, Green S, Beaumont H, Burns A, Moll J, Caine D, et al. Frontotemporal lobar degeneration and social behaviour: dissociation between the knowledge of its consequences and its conceptual meaning [Internet]. *Cortex* 2017

Zahn R, Moll J, Iyengar V, Huey ED, Tierney M, Krueger F, et al. Social conceptual impairments in frontotemporal lobar degeneration with right anterior temporal hypometabolism. *Brain* 2009; 132: 604–616.

Legends

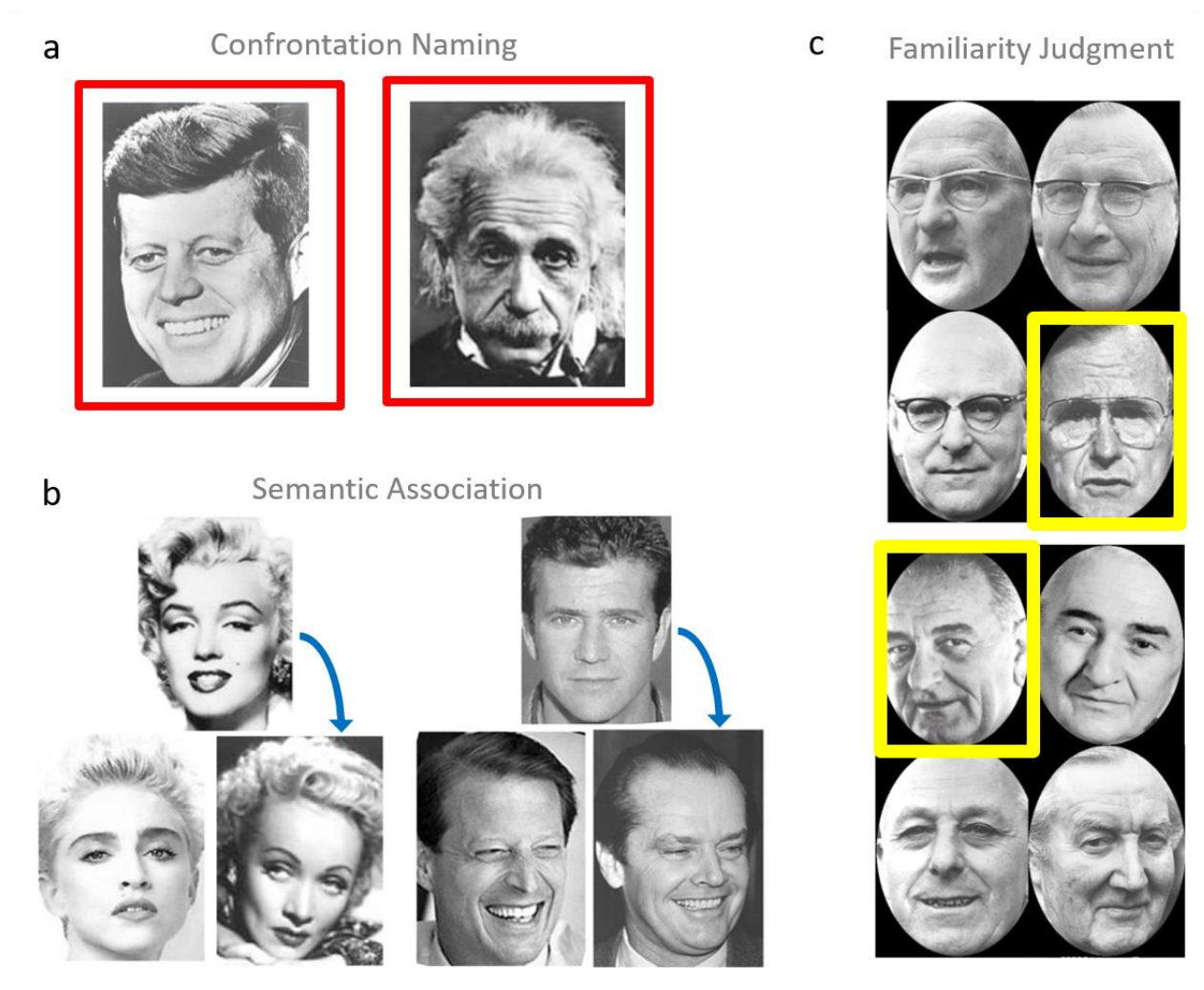


Figure 1 UCSF Famous Faces Battery. a) Two examples of the stimuli used in the Confrontation Naming task, where subjects are asked to retrieve the proper name of each famous face presented. b) Two examples of the stimuli used in the Semantic Association task, in which subjects have to select, among three famous faces, the two sharing a semantic connection (i.e., being in the same profession). c) Two examples of the stimuli used in the Familiarity Judgment task, where subjects are asked to select the familiar face among three unfamiliar distractors.

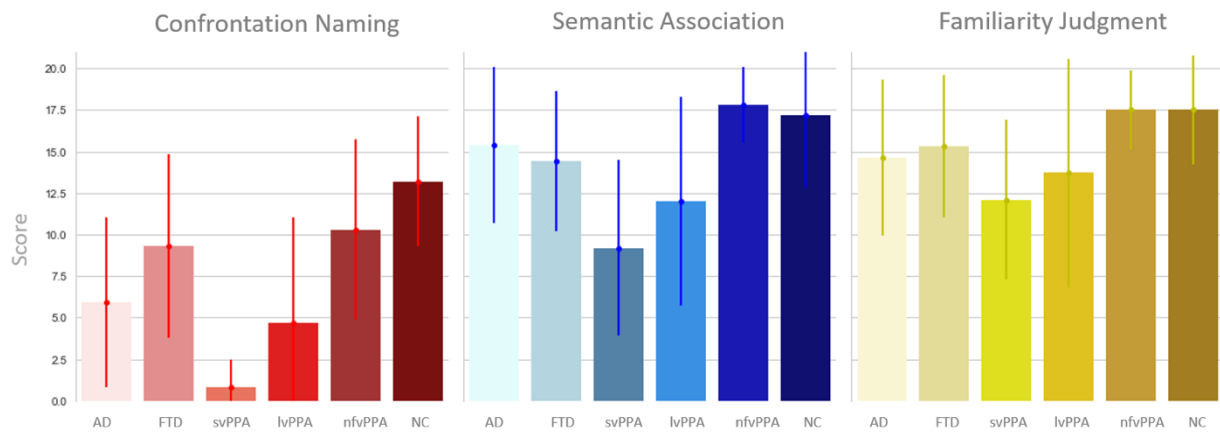


Figure 2 Famous face processing breakdown in neurodegenerative disorders. The results of the three tasks of the UCSF Famous Faces Battery allow descriptive comparisons of famous face processing deficits across different clinical profiles [average across clinical spectra, error bars represent standard deviation]. See Table 1 for details. AD = Alzheimer’s disease spectrum; FTD = frontotemporal dementia spectrum; svPPA = semantic variant Primary Progressive Aphasia; lvPPA = logopenic variant Primary Progressive Aphasia; nvfPPA = nonfluent variant Primary Progressive Aphasia.

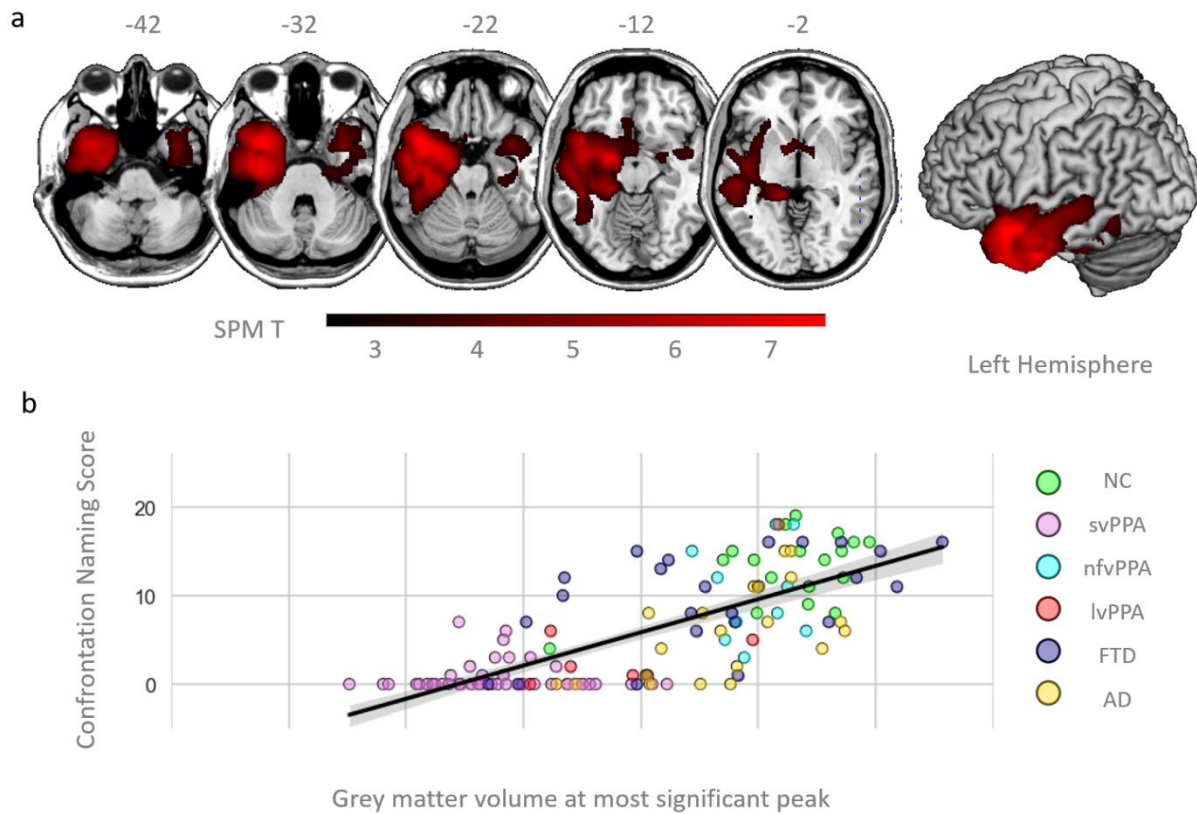


Figure 3 Brain regions associated with famous face naming performance. a) Voxel-based morphometry identify regions of GM atrophy that correlated with performance in the Confrontation Naming task across all 123 participants ($p < .001$, FWE-corrected at the cluster level). b) For descriptive purposes, behavioral scores are plotted as a function of grey matter volumes at the most significant cluster [colors indicate the different clinical groups].

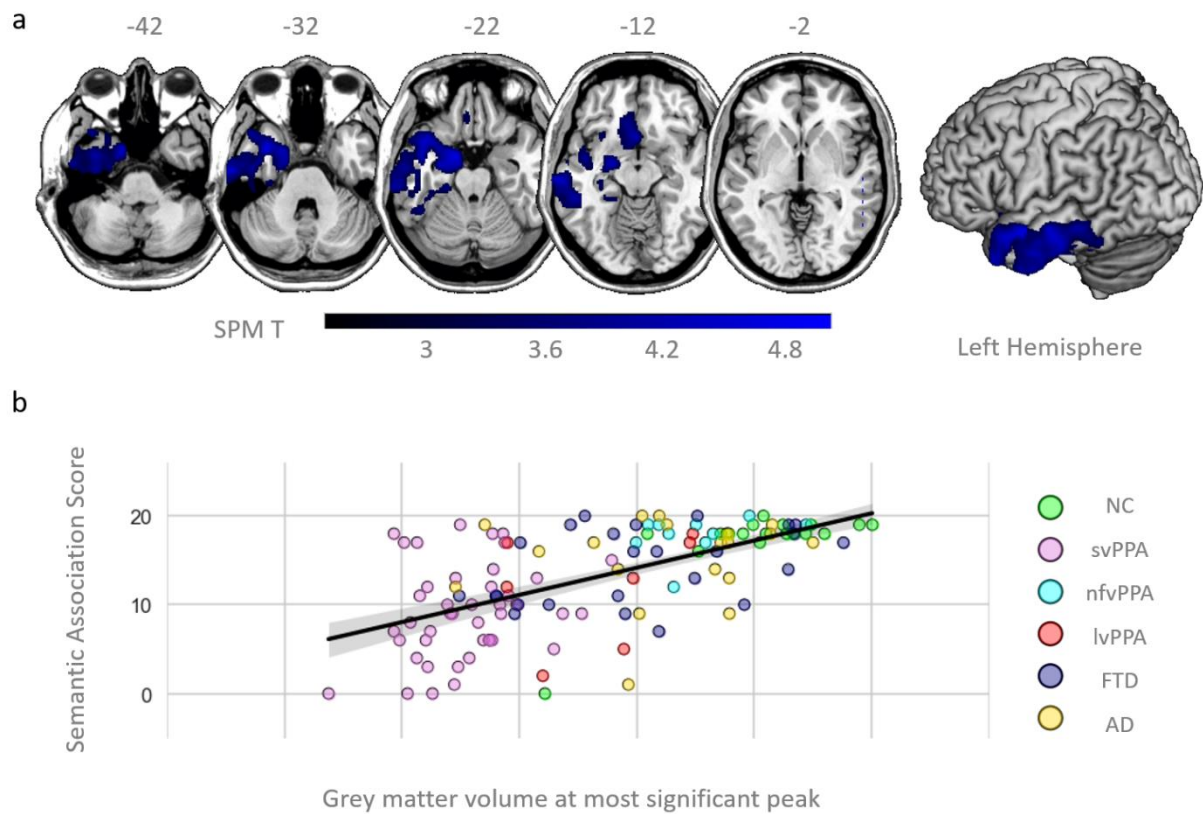


Figure 4 Brain regions associated with famous face semantic retrieval. a) The results of the voxel-based morphometry analyses conducted across 123 participants demonstrates the correlation between left-sided temporal pole GM volume and the performance in the Semantic Association task $p < .001$, FWE-corrected at the cluster level). b) For descriptive purposes, behavioral scores are plotted as a function of grey matter volumes at the most significant cluster [colors indicate the different clinical groups].

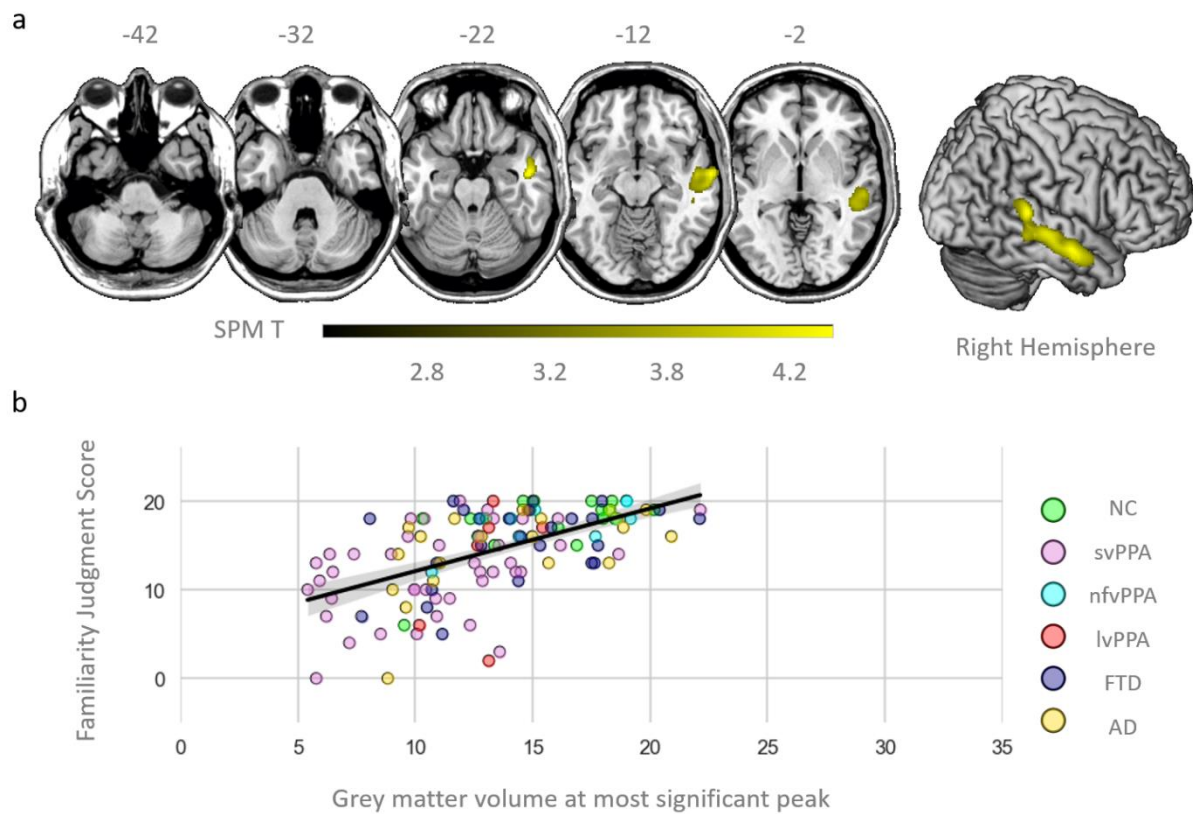


Figure 5 Brain regions associated with famous face familiarity judgment. a) Voxel-based morphometry identify regions of GM atrophy that correlated with performance in the Familiarity Judgment task across all participants ($p < .001$, FWE-corrected at the cluster level). b) For descriptive purposes, behavioral scores are plotted as a function of grey matter volumes at the most significant cluster [colors indicate the different clinical groups].

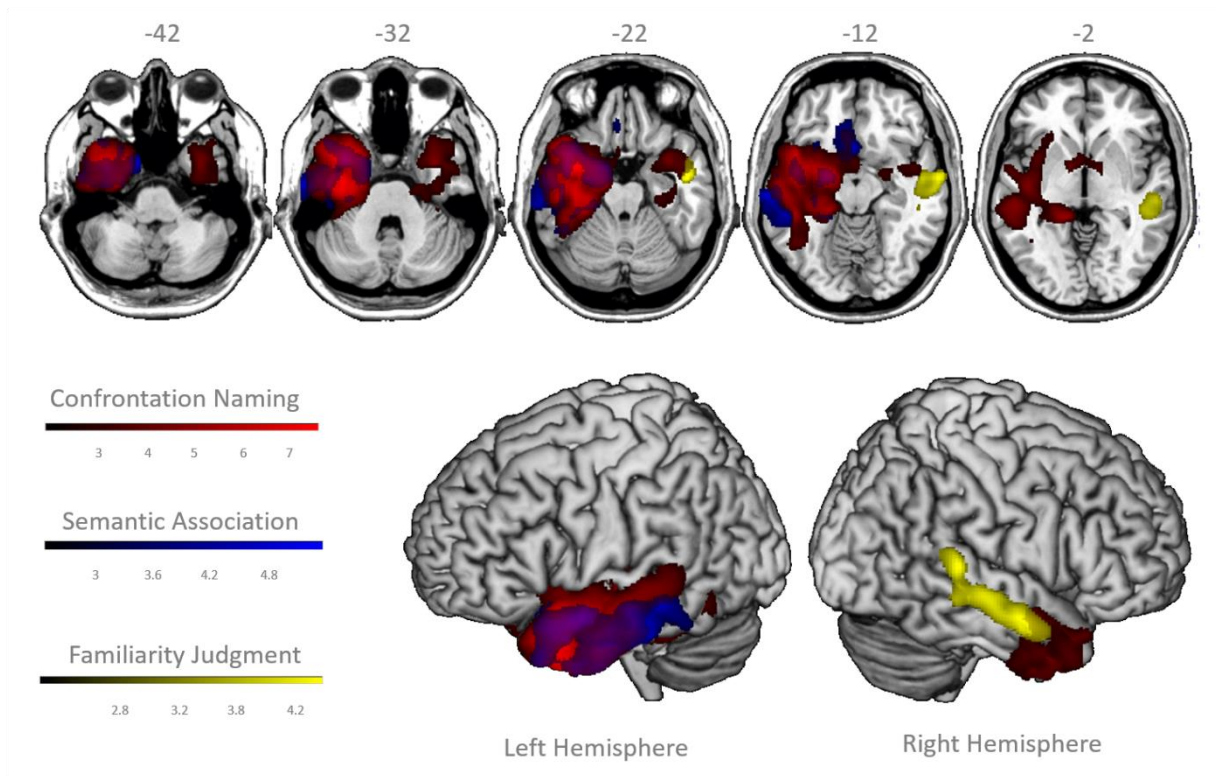


Figure 6 Isolating naming, semantic retrieval, and familiarity judgment. The three effects are overlaid on five axial slices and a rendered template brain (left and right hemisphere).

TABLE 1. Behavioral and cognitive results

	svPPA	lvPPA	nvfPPA	AD Spectrum	FTD Spectrum	NCs
	n = 43 Mean (SD)	n = 7 Mean (SD)	n = 10 Mean (SD)	n = 20 Mean (SD)	n = 25 Mean (SD)	n = 18 Mean (SD)
Demographic Data and Cognitive Profile						
Age	65.3(8.4)	63.6(8.5)^	66.4(10.3)	58.2(6.3)	60.8(7.1)	67.1(10.4)
Clinical Dementia Rating	1.0(.6)§	.8(.6)	.4(.3)	.8(.5)	1.0 (.6)	.2(.4)
MMSE (30)	22.6(6.4)	17.7(8.2)	26.2(3.6)	23.6(5.5)	25.5(5.3)	29.1(1.5)
<i>Memory</i>						
CVLT-SF Trials 1-4 Total (36)	16.9(7.4)§	13.9(8.7)^	27.9 (3.6)	19.4(9.5)	20.8 (7.4)	28.5(6.0)
CVLT-SF 30" Delay (9)	2.9(2.6)§	3.1(2.3)^	7.3 (1.5)	4.2(3.5)	5.1 (2.7)	7.8(1.9)
CVLT-SF 10' Delay (9)	1.9(2.5)§	2.7(2.9)^	7.3(1.7)	3.6(3.6)	4.3(3.0)	7.5(1.9)
Benson Copy 10' Delay (17)	5.6(4.7)§	5.3(4.8)	11.0(2.9)	7.0(6.0)	8.0(4.4)	12.9(4.1)
<i>Visuospatial/Visuoconstruction</i>						
Benson Figure Copy (17)	15.2(1.5)	10(6.2)^	16.1(1.1)	11.6(6.3)	14.0(3.0)	15.8(1.6)
Calculations (5)	4.2(1.0)†	2.8(1.8)^	4.5(.8)	3.6(1.6)	4.1(1.3)	4.7(.7)
Affect Naming (16)	9.9(3.5)	12°	9°	14.0(2.8)	10.7(3.3)	N/A
<i>Executive Functions</i>						
Digit Span Forward	6.6(1.5)	N/A	N/A	8.0°	4.5(.7)	N/A
Digit Span Backward	4.9(1.3)†§	3(.9)	3(.8)	3.9(1.4)	4.2(1.8)	5.3(1.5)
Modified Trails Completion Time (in seconds)	57.2(34.1)†	108.8(27.4)	74(43.7)	82.0(43.0)	64.7(40.9)	33.3(23.5)
Design Fluency	7.0(3.6)	7(3.5)	8.5(3.0)	5.8(4.0)	6.2(3.7)	10.9(3.0)
<i>Language</i>						
Animal Fluency	7.7(5.0)	9.3(5.5)	10.9(5.5)	11.9(6.7)	11.8(5.9)	22.1(7.0)
Lexical Fluency	7.7(4.2)§	6.8(6.1)	5.9(4.0)	8.9(5.1)	8.9(6.5)	16.6(4.1)
Abbreviated BNT (15)	4.8(3.9)†	8.7(3.8)^	12.8(2.5)	11.5(3.3)	12.3(2.3)	14.3(1.7)
WRAT-4 Reading (70)	56.8(9.3)	N/A	N/A	58.0°	60(0.7)	N/A
Syntax Comprehension (5)	4.2(.9)§†	1.8(1.7)	3.3(.5)	3.7(1.6)	3.7(1.5)	4.7(.7)
Verbal Agility (6)	5.1(1.5)	3.8(2.1)	3.5(2.1)	4.5(1.8)	4.6(1.2)	5.5(.8)
Repetition (5)	3.4(1.4)†	2.0(.8)	2.5(1.9)	3.6(1.3)	3.9(1.0)	4.5(1.3)
PPVT (16)	8.4(3.9)†§	14.7(1.5)	14.2(1.9)	13.6(1.9)	14.0(2.2)	15.5(.8)
Pyramids and Palm Trees	39.5(7.5)	N/A	48.7(1.5)	N/A	44.5(6.4)	40°
Benton Faces (% correct)	76%(22%)	55%(48%)	65%(44%)	74%(11%)	67%(30%)	64%(34%)
Experimental Battery						
<i>UCSF Famous Face Battery</i>						
Confrontation Naming (20)	.8(1.7)†§	4.7(6.3)^	10.3(5.4)	5.9(5.1)	9.3(5.5)	13.2(3.9)
Semantic Association (20)	9.2(5.3)§	12.0(6.3)^	17.8(2.3)	15.4(4.7)	14.4(4.2)	17.2(4.4)
Familiarity Judgment (20)	12.1(4.8)§	13.7(6.9)	17.5(2.4)	14.6(4.7)	15.3(4.3)	17.5(3.3)

CDR, Clinical Dementia Rating; CVLT-SF, California Verbal Learning Test-Short Form; MMSE, Mini Mental State Exam; WRAT-4, Wide Range Achievement Test-4; PPVT, Peabody Picture Vocabulary Test; AD, Alzheimer's disease; FTD, Fronto-Temporal Dementia; svPPA, semantic variant Primary Progressive Aphasia; Primary Progressive Aphasia; lvPPA, logopenic variant Primary Progressive Aphasia; nvfPPA, nonfluent variant

° N=1; * p<.05 vs. NC; † p<.05 svPPA vs. lvPPA; § p<.05 svPPA vs. nvfPPA; ^ p<0.5 lvPPA vs. nvfPPA;

Table 2. Coordinates of voxel-based morphometry analysis of Famous Faces Battery							
	Max T	x	y	z	Z score	p _{FWE-corr}	K _E
Confrontation Naming							
Left Temporal Pole	T = 7.98	-42	8	-21	7.11	0.00	48338
Semantic Association							
Left Temporal Pole	T = 5.01	-15	0	-20	4.75	0.00	17820
Familiarity Judgment							
Right Middle Temporal Gyrus	T = 4.21	50	-7	-20	4.05	0.00	3079

K_E = number of voxels; p_{FWE-corr} = FWE corrected p-value at the cluster level; Max T = maximum T statistic at each peak.

Suppl. Table 1. Behavioral and cognitive results of left vs right variants of svPPA				
	svPPA	Left - svPPA	Right - svPPA	NCs
	n = 43	n = 28	n = 15	n = 18
	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)
Demographic Data and Cognitive Profile				
Age	65.3(8.4)	65.0(9.0)	65.9(7.5)	67.1(10.4)
Clinical Dementia Rating	1.0(.6)§	.9(.6)	.8(.4)	.2(.4)
MMSE (30)	22.6(6.4)	20.7(7.0)*	26.1(2.7)	29.1(1.5)
<i>Memory</i>				
CVLT-SF Trials 1-4 Total (36)	16.9(7.4)§	15.2(7.7)*	20.1(5.6)	28.5(6.0)
CVLT-SF 30" Delay (9)	2.9(2.6)§	2.4(2.7)	3.9(2.2)	7.8(1.9)
CVLT-SF 10' Delay (9)	1.9(2.5)§	1.5(2.5)	2.6(2.6)	7.5(1.9)
Benson Copy 10' Delay (17)	5.6(4.7)§	5.9(5.2)	5.1(3.9)	12.9(4.1)

Visuospatial/Visuoconstruction

Benson Figure Copy (17)	15.2(1.5)	15.0(1.5)	15.5(1.3)	15.8(1.6)
Calculations (5)	9.9(3.5)	10.3(3.6)	9.0(3.4)	N/A
Affect Naming (16)	76%(22%)	73%(26%)	81%(9%)	64%(34%)

Executive Functions

Digit Span Backward	4.9(1.3)‡§	4.7(1.1)	5.2(1.5)	5.3(1.5)
Modified Trails Completion Time (in seconds)	57.2(34.1)‡	53.5(37.1)	63.9(27.9)	33.3(23.5)
Design Fluency	7.0(3.6)	7.4(3.7)	6.5(3.5)	10.9(3.0)

Language

Animal Fluency	7.7(5.0)	6.2(4.8)*	10.1(4.4)	22.1(7.0)
Lexical Fluency	7.7(4.2)§	7.4(3.5)	8.2(5.2)	16.6(4.1)
Abbreviated BNT (15)	4.8(3.9)†	3.4(3.3)**	7.4(3.6)	14.3(1.7)
WRAT-4 Reading (70)	56.8(9.3)	55.5(9.8)	59.2(8.6)	N/A
Syntax Comprehension (5)	4.2(.9)§‡	4.0(1.0)	4.5(.7)	4.7(.7)
Verbal Agility (6)	5.1(1.5)	5.3(1.5)	4.9(1.4)	5.5(.8)
Repetition (5)	3.4(1.4)†	3.3(1.5)	3.7(1.1)	4.5(1.3)
PPVT (16)	8.4(3.9)†§	7.2(3.9)*	10.4(3.0)	15.5(.8)
Pyramids and Palm Trees	39.5(7.5)	38.9(6.7)	40.6(9.0)	40°

Experimental Battery

UCSF Famous Face Battery

Confrontation Naming (20)	.8(1.7)‡§	.7(1.6)	.9(1.9)	13.2(3.9)
---------------------------	-----------	---------	---------	-----------

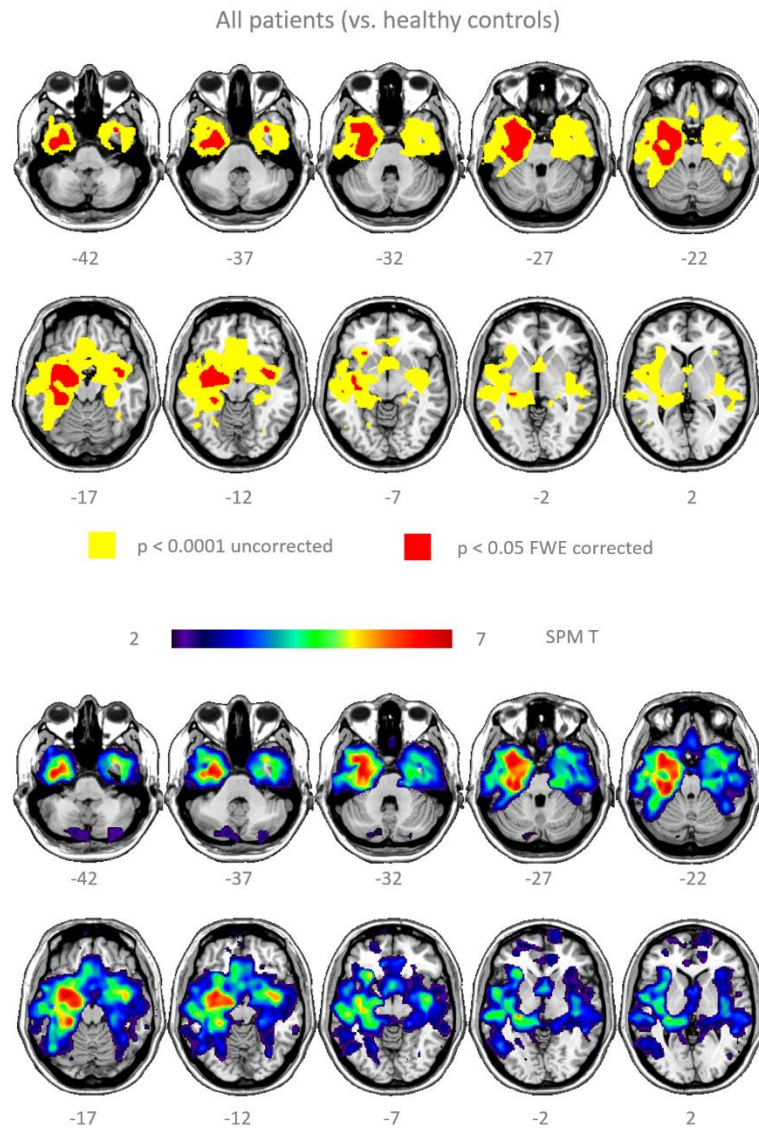
Semantic Association (20)	9.2(5.3)§	9.1(6.1)	9.5(3.3)	17.2(4.4)
Familiarity Judgment (20)	12.1(4.8)§	13.6(4.3)**	9.3(4.5)	17.5(3.3)

CDR, Clinical Dementia Rating; CVLT-SF, California Verbal Learning Test-Short Form; MMSE, Mini Mental State Exam;

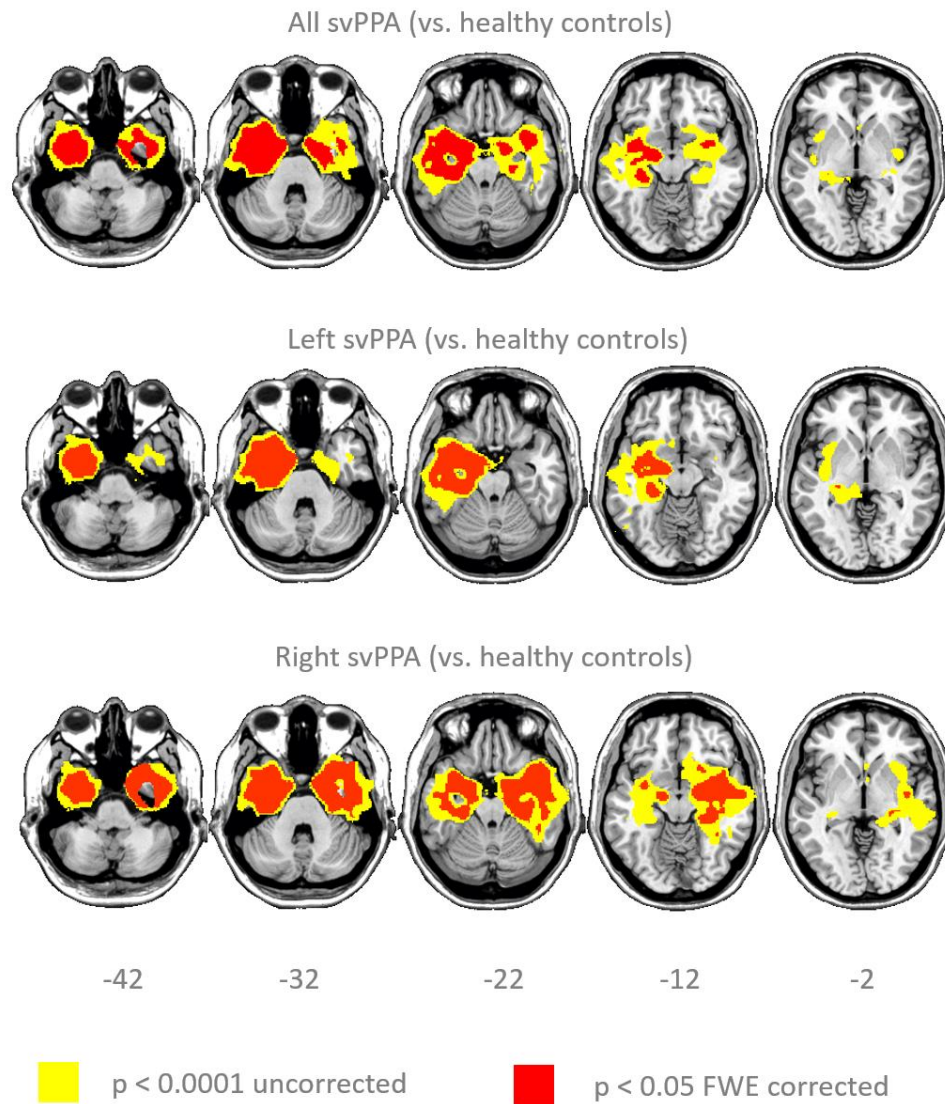
WRAT-4, Wide Range Achievement Test-4; PPVT, Peabody Picture Vocabulary Test;

svPPA, semantic variant Primary Progressive Aphasia;

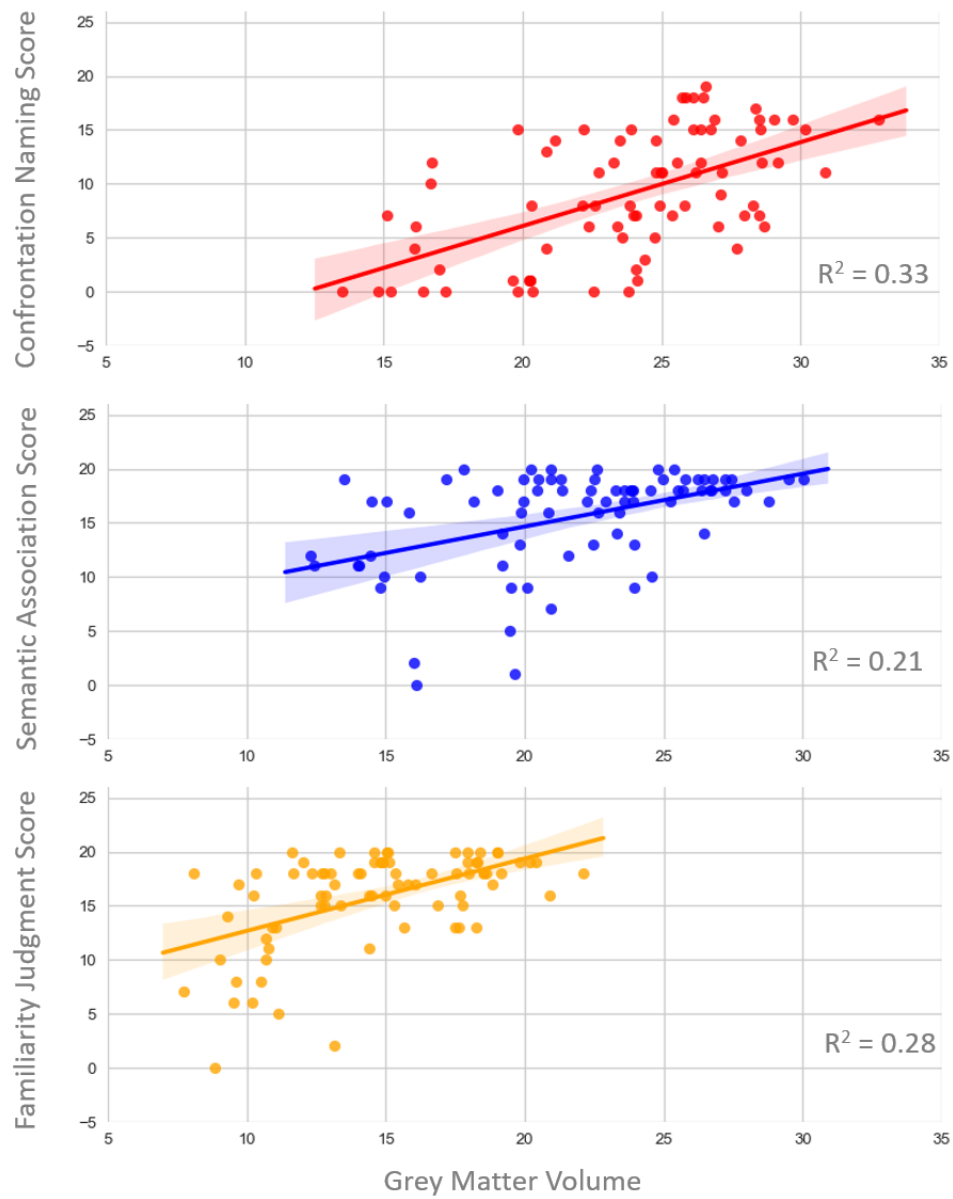
^aN=1, *p<0.05; rSD vs. ISD; **p<0.01; rSD vs. ISD



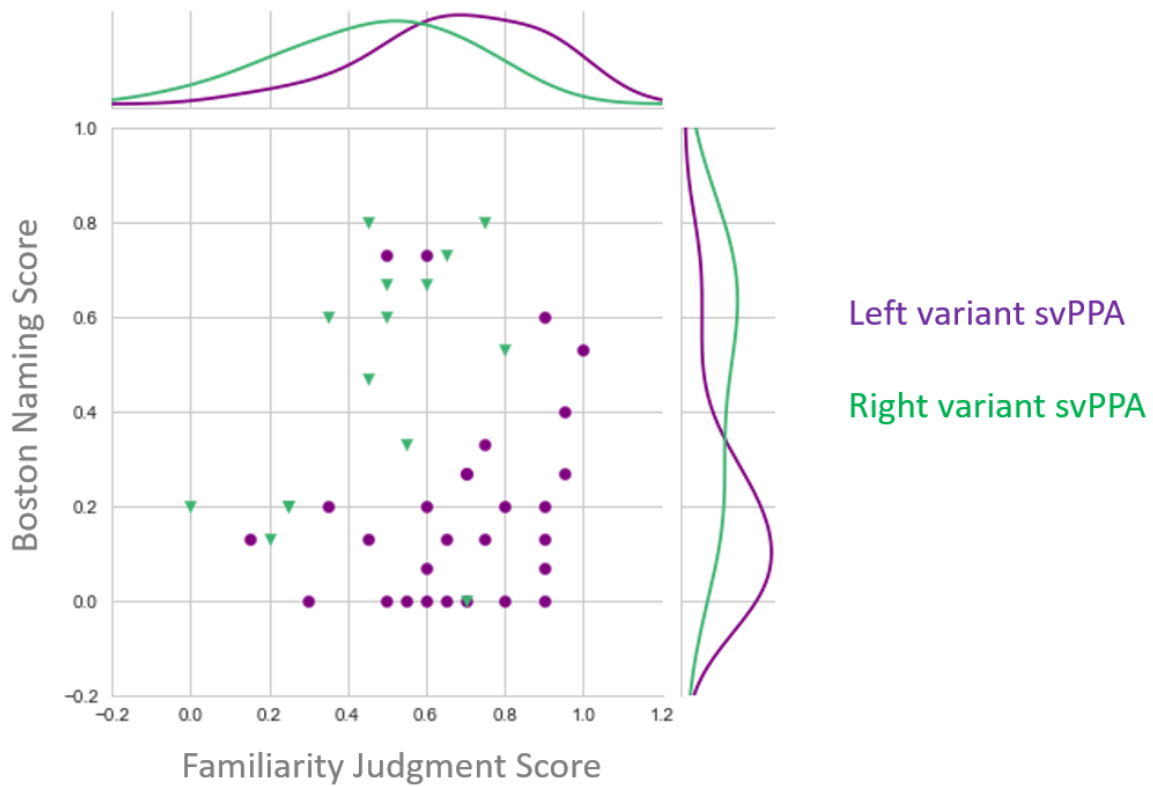
Supplementary Figure 1 Atrophy map of patients' cohort. Voxel-based morphometry maps showing atrophy patterns for all patients included in the study (n=105). Maps are thresholded at $p < 0.0001$ uncorrected (yellow) and $p < 0.05$ family-wise error (FWE) corrected (two upper rows). For descriptive purposes, SPM T maps are also reported (two lower rows). Covariates: age, gender, education, TIV, CDR, and scanner type.



Supplementary Figure 2 Atrophy map of svPPA patients. Voxel-based morphometry maps showing atrophy patterns for all svPPA patients ($n=43$, upper row), the subset of left svPPA ($n=28$, middle row), and the subset of right svPPA ($n=15$, bottom row). Maps are thresholded at $p < 0.0001$ uncorrected (yellow) and $p < 0.05$ family-wise error (FWE) corrected. Covariates: age, gender, education, TIV, CDR, and scanner type.



Supplementary Figure 3 Correlations without svPPA. Correlation plot of scores in naming (red), semantic association (in blue) and familiarity judgement (in yellow) vs. grey matter volumes (in the same clusters as Figure 3,4 and 5 respectively) after removing svPPA patients. All correlations are significant with $p < 0.001$.



Supplementary Figure 4 Dissociating left vs right svPPA profiles. Scatter plot and density distribution graph for the two variants of svPPA illustrating the relation between the performance at the Boston Naming Task and the Famous Face Familiarity Judgment Task (for both tasks, scores represent percentage correct for each participant).